Published in final edited form as:
J Hum Lact. 2007 May ; 23(2): 184–190. doi:10.1177/0890334407300336.

Concentrations of Methadone in Breast Milk and Plasma in the Immediate Perinatal Period

Lauren M. Jansson, MD [Director of pediatrics],
Center for Addiction and Pregnancy, Baltimore, MD.

Robin E. Choo, PhD [Completing a postdoctoral fellowship],
National Institute on Drug Abuse, Baltimore, MD.

Cheryl Harrow, RNC, IBCLC, MSN, CRNP [Family nurse practitioner and international board-certified lactation consultant],
Johns Hopkins Bayview Medical Center full-term nursery, Baltimore, MD.

Martha Velez, MD [Provides care to substance abusing women and their children],
Center for Addiction and Pregnancy, Baltimore, MD.

Jennifer R. Schroeder, PhD [Biostatistician],
National Institute on Drug Abuse intramural clinical research program, Baltimore, MD.

Ross Lowe, PhD [Research scientist], and
Chemistry and Drug Metabolism Section, IRP, NIDA, NIH, Baltimore, MD.

Marilyn A. Huestis, PhD [Tenured senior investigator]
National Institute on Drug Abuse, Baltimore, MD.

Abstract

This study evaluates concentrations of methadone in breast milk and plasma among a sample of methadone-maintained women in the immediate perinatal period. Twelve methadone-maintained, lactating women provided blood and breast milk specimens 1, 2, 3, and 4 days after delivery. Specimens were collected at the time of trough (just before methadone dose) and peak (3 hours after dosing) maternal methadone levels. Paired specimens of foremilk (prefeed) and hindmilk (postfeed) were obtained at each sampling time. Although there was a significant increase in methadone concentration in breast milk over time for the peak postfeed sampling time, $t(22) = 2.40$, $P = .0255$, methadone concentrations in breast milk were small, ranging from 21 to 314 ng/mL, and were unrelated to maternal methadone dose. Results obtained from this study contribute to the recommendation of breastfeeding for methadone-maintained women regardless of methadone dose.

Keywords

methadone; breastfeeding; lactation; breast milk

Methadone maintenance has been recognized as the optimal treatment for opiate dependency during pregnancy and in the postpartum period.[1] In appropriate doses, methadone therapy confers major advantages for pregnant women, including diminished illicit opioid use,[2-4] the provision of an avenue for substance abuse treatment,[5] improved attention to outstanding

Address correspondence to Lauren M. Jansson, MD, Johns Hopkins University School of Medicine, The Center for Addiction and Pregnancy, JHBMC, D5, 4940 Eastern Avenue, Baltimore, MD 21224; E-mail: ljansson@jhmi.edu..

maternal medical care needs and nutrition,[6] and the creation of a more stable environment for the infant.[6,7] In addition, methadone maintenance provides the infrastructure for receiving parenting training, which has been found to improve parenting knowledge and skills among this population.[8,9] Although its use has proven benefits for mothers, methadone-exposed infants are at risk for multiple difficulties in the neonatal period, most notably neonatal abstinence syndrome (NAS), manifested in more than 60% of these infants.[10] Compared to their non-drug-exposed cohorts, methadone-exposed infants are smaller in size,[11] more frequently display sleeping disorders,[12] and are at higher risk for decreased maternal attachment.[13]

It is well established that breastfeeding is the optimal way to nourish an infant.[14-17] Breast milk confers a number of known advantages to the mother and infant[18] and could be most beneficial for the vulnerable group of methadone-exposed infants who are at risk for morbidity in the perinatal period. The American Academy of Pediatrics classifies methadone as a drug usually compatible with breastfeeding and reports no adverse signs or symptoms in breastfed infants of methadone-maintained mothers.[19] Yet multiple barriers exist that frequently prevent this group of women from breastfeeding, including those imposed by health care providers due to lack of clear guidelines, by feeding problems exhibited by drug-exposed infants experiencing acute or subacute NAS, and by the opioid-dependent women themselves due to poor self-esteem, lack of knowledge, or feelings of guilt.[20] Recommendations regarding breastfeeding among methadone-maintained women have ranged from avoidance of breastfeeding for all such women[21] to using breast milk of methadone-maintained women to treat NAS,[22] with most authors recommending breastfeeding for methadone-maintained women, if desired, under certain circumstances.[23-29] Guidelines for methadone-maintained women desiring to breastfeed their infants vary by region, hospital, and provider. Not uncommonly, methadone-maintained women wishing to breastfeed their infants after delivery are given conflicting advice by different treatment providers during the course of a single hospitalization.

There is a paucity of information regarding breast milk and methadone maintenance to date, with only a handful of studies published over the past 30 years. Despite small sample sizes (numbers of participants ranging from 1 to 12) and widely variable sample collection protocols and analysis techniques, in general, the mean concentration of methadone in human milk has been reported as ranging from 50 to 270 ng/mL; methadone exposure for the infant ranges from 0.01 to 0.09 mg/day.[23-29] Postfeed breast milk methadone concentrations are approximately 33% higher than prefeed concentrations; this is most likely due to the increase in lipid content in breast milk that occurs during the course of a feeding.[28] This study evaluates methadone content in breast milk in the immediate postnatal period, its relationship to maternal dose and plasma concentrations, and the variability in breast milk methadone concentrations in fore- and hindmilk.

Methods

Participants

Participants were pregnant women enrolled in a comprehensive substance abuse treatment program (described elsewhere[30]), enrolled from a larger, longitudinal study evaluating the effects of methadone in breast milk on infant neurobehavior. For the parent study, 2257 women were screened over a 5-year period for the following criteria: opiate dependence, meeting federal guidelines for methadone maintenance, expressing a desire at routine obstetric care visits to breastfeed their infants, once-daily methadone dose, and uncomplicated singleton pregnancy (ie, HIV-negative status, fetal measurements appropriate for gestational age, absence of fetal malformations, and without significant pregnancy complications such as gestational diabetes and hypertension). Participants were then selected for participation based on recommendation from their counselors for compliance to program standards, absence of

evidence of licit or illicit drug use in the prior month of treatment (defined as a positive breathalyzer, positive urine toxicology, or presumed positive [appearing under the influence of licit or illicit substances] toxicology), and staff confidence in their ability to maintain their abstinence in the postpartum period. Fifty-eight women met enrollment criteria and were enrolled in the parent study at 36 weeks gestation. Women completing days 1 through 4 of data collection composed the study population presented. Gestational dating was determined by a prenatal ultrasound around the 20th week of gestation as per program standards. The breastfeeding methadone-maintained women were generally not different demographically (parity, age) or by substance use history from program participant means for women meeting criteria for methadone maintenance. However, there was a greater preponderance of Caucasian women in the sample, which may reflect cultural preferences for breastfeeding.[31,32] Women were excluded from study participation for relapse to licit or illicit substances consequent to enrollment at 36 weeks gestation, premature birth (less than 37 weeks estimated gestational age at delivery), delivery by cesarean section (which typically involves medications for pain), or formula supplementation for breastfeeders during the study period. Twelve women over the 5-year project period were able to participate in the study in the immediate postpartum period (days 1 though 4). All study participants were placed on a morning (10:00 AM to 11:00 AM) methadone-dosing schedule 1 month prior to delivery and monitored per program standards for licit and illicit drug use. Monitoring included a minimum of weekly random urine toxicology tests for opiates, cocaine, benzodiazepines, alcohol, cannabinoids, phencyclidine, and methadone. Women appearing under the influence of any substance or who had a positive urine toxicology test were excluded from study participation. Additionally, standard care required urine toxicology tests for all participants and their infants at birth. The research was approved by the governing institutional review board (Johns Hopkins Medicine IRB 1), and written informed consent was obtained from all participants.

Study Procedures

Breastfeeding women submitted 4 (paired pre- and postfeed) specimens of breast milk 1, 2, 3, and 4 days after delivery. Breast milk pre- and postfeed samples were obtained from a single breast at each sampling time, identified as the breast not used last in the prior feeding. The infant was fed from this breast between the pre- and postfeed samples, with an effort made to empty the breast as completely as possible. Days of life were determined by the 24-hour daytime period nearest the delivery time, keeping the determined day of life as close as possible to the infant's actual day of life. Further manipulation of the designated days of life was not possible due to methadone dosing restrictions; women continued to be medicated at 10:00 AM throughout the study period. Specimens were collected at times of trough (just prior to single daily oral methadone dose) and at peak (3 hours after single daily methadone dose) maternal methadone levels. Peak plasma methadone levels in individuals chronically treated with oral methadone occur between 2 and 4 hours after an oral daily dose.[33] Paired specimens consisted of breast milk expressed (by hand or electric pump) just prior to breastfeeding (foremilk) and breast milk expressed after the infant had ceased breastfeeding (hindmilk) from the same breast. All women gave blood specimens at trough and peak maternal methadone levels. Participants' perceived symptomatology indicative of opiate withdrawal was surveyed at each trough and peak test session, using the Subjective Opiate Withdrawal Scale (SOWS).[34] Methadone administration was confirmed by pupil-lometer photograph, using a modified Polaroid One-Step camera (Polaroid, Waltham, MA), which revealed pupillary constriction at peak (vs trough) in all cases.

Laboratory Analysis of Breast Milk and Plasma

Breast milk was collected in polypropylene storage vials and stored at −20°C until time of analysis. Specimens were analyzed using a validated liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry method. Briefly, 0.5 mL of breast milk

was analyzed utilizing an LCQ Deca XP Ion Trap Mass Spectrometer (ThermoFinnigan, San Jose, CA), following protein participation and solid phase extraction (SPE). Identification and quantification of methadone was based on selected reaction monitoring. The limit of quantification (LOQ) was 10 ng/mL, with a linear dynamic range of 10 to 500 ng/mL. Extraction efficiency was greater than 97%, with inter- and intraday imprecision < 20%.

Blood was collected in vacutainer green-top vials containing heparin. After centrifugation, plasma was separated from red blood cells and stored at −20°C in polypropylene tubes until time of analysis. Plasma specimens were analyzed by gas chromatograph mass spectrometry (Agilent, Dover, DE) following SPE, using modifications of the methods of Galloway (1999) [35] and Alburges (1996).[36] The LOQ for methadone was 5.0 ng/mL, and the range of linearity was 5 to 2000 ng/mL. Imprecision was < 20% for the method.

Calculation of Mean Infant Dose Ingestible

Mean infant methadone exposure was calculated from the average of pre- and postfeed breast milk methadone concentrations per day and extrapolated to the total methadone dose ingestible per day. Average breast milk yield volumes per day of life were obtained from previously published research.[37]

Analysis

Basic descriptive statistics (mean, standard deviation, range) were calculated to describe the study sample in terms of maternal demographic characteristics, birth outcomes, concentrations of methadone in breast milk and plasma, and ratios of breast milk methadone to plasma methadone (BM/P). Due to the small sample size, Spearman correlation coefficients were used to assess the strength of association between methadone concentrations in breast milk and plasma, and between maternal methadone dose and BM/P, at times relative to methadone dose (peak and trough, days 1 through 4). Repeated measures linear regression was used to determine whether there was a significant change over time in breast milk methadone concentrations for each sampling time (trough prefeed, trough postfeed, peak prefeed, peak postfeed). All analyses were done using SAS statistical software (version 9, SAS Institute, Cary, NC). Statistical significance was set at $P < .05$ for all analyses.

Results

Mothers

The mean (± SD) maternal age was 27.2 ± 4.3 years; 9 women were Caucasian and 3 African American; 4 were primiparous. Four required psychotropic medications during pregnancy (sertraline [2], fluoxetine [2], and olanzapine [1]; 1 woman required 2 medications). Mean (± SD) methadone dose at delivery was 75.8 ± 22.1 mg (range 40-110 mg). Mean SOWS scores at trough and peak maternal methadone levels averaged 4.0 to 5.6, and all were 16 or below, reflecting no or little subjective reporting of withdrawal symptoms.[34]

Infants

All infants (5 males, 7 females) were term at delivery, with birth parameters appropriate for gestational age (birth weight mean [± SD] 3061.3 gm ± 437.2 gm, length 50.0 cm ± 2.7 cm, head circumference 32.8 cm ± 1.8 cm). Mean 1- and 5- minute Apgar scores were 8.3 and 8.9. Only 1 infant required pharmacologic treatment of mild to moderate NAS, with a total hospitalization of 10 days (6 for NAS treatment).

Breast Milk

Breast milk yield was expectedly variable on days 1 and 2, as amounts of colostrum able to be expressed are typically small.[38] Minimum, maximum, and mean concentrations of methadone in breast milk by day are presented in Table 1.

The calculated average dose of methadone ingestible by the infant from breast milk each day was 0.006 mg on day 1, 0.018 mg on day 2, 0.039 mg on day 3, and 0.084 mg on day 4. Repeated measures linear regression showed a significant increase in breast milk methadone concentrations over time for the peak postfeed sampling time, $t(22) = 2.40$, $P = .0255$. Changes in breast milk methadone concentrations over time did not attain statistical significance for the other 3 sampling times.

Plasma

Minimum, maximum, and mean concentrations of methadone in maternal plasma by day are presented in Table 2. Spearman correlations between breast milk and plasma methadone concentrations ranged from .09 (day 2 trough) and .47 (day 4 peak); no correlations differed significantly from zero. Mean concentrations of plasma and breast milk methadone are presented in Figure 1.

Breast Milk/Plasma Methadone Ratios

Breast milk methadone to plasma methadone (BM/P) concentration ratios for all 8 sampling times (trough and peak, days 1-4) are presented in Table 3. BM/P ratios at trough maternal methadone levels ranged from 0.1 to 2.7; BM/P ratios at peak maternal methadone levels ranged from 0.1 to 1.2.

Discussion

This study evaluated the concentration of methadone in maternal plasma and breast milk at trough and peak maternal methadone levels on consecutive days in the immediate postnatal period. Consistent with previously published reports,[23-29] the concentration of methadone in breast milk was small, ranging from 20.6 to 314.2 ng/mL. Methadone concentrations in breast milk were unrelated to maternal dose. Concentrations increased from pre- to postfeed in all cases aside from the first collection (trough, day 1) by a mean of 10.5%, which is at the lower end of the range (10%-56%, mean 33%) previously reported by Wojnar-Horton[28] using breast milk from 12 women with older infants (age range 3-26 days). This is likely due to the increasing fat content in milk over the course of a feeding; hindmilk, or the final two thirds of the volume of milk excreted during a feed is higher in fat content than foremilk, the first one-third of the volume excreted.[39] Another important factor is the lipophilic nature of methadone.[28] Similarly, fat content in human milk increases over the first 28 days of lactation,[40] which may explain the lower mean increase in methadone concentration in breast milk in the first 4 days as compared to breast milk of women with older infants. A comparison of average (pre- and postfeed) trough to average (preand postfeed) peak methadone concentrations in breast milk yielded increasing concentrations of methadone in breast milk: by 50.6% on day 2, 48.6% on day 3, and 68.8% on day 4. Calculations of methadone available for ingestion by the infant in this period are difficult, due to the variable nature of colostrum intake among newborns. However, using mean breast milk volumes calculated from previous research,[37] and averages of breast milk methadone concentrations across all 4 sampling periods per day, the calculated average dose of methadone ingestible by the infant ranged from 0.006 mg on day 1 to 0.084 mg on day 4. This range is consistent with previously published reports.[23-29]

Maternal plasma methadone concentrations expectedly increased from trough to peak sampling times. There were no significant correlations between maternal methadone dose and peak or

trough maternal plasma methadone concentrations at any sampling time ($P > .05$). This is contrary to published reports in men and nonpregnant women[41] but consistent with other reports in pregnant subjects[24] and may be due to the changing pharmacokinetics of methadone metabolism during gestation.[26,42] There were also no significant correlations between maternal methadone dose and trough or peak breast milk methadone concentrations at any sampling time ($P > .05$). Maternal plasma methadone concentrations were similarly unrelated to maternal breast milk methadone concentrations at any of the 4 sampling times ($P > .05$).

Breast milk to plasma ratios were lower at peak (mean 0.44) than at trough (mean 0.74). These ratios were not dependent on maternal methadone dose, nor were they dependent on maternal plasma methadone concentrations. Although there was no relationship between BM/P and maternal breast milk concentration on days 1 and 2, there was a significant relationship between BM/P and maternal breast milk trough and peak methadone concentrations on days 3 and 4. This may be due to the relatively small numbers of participants with both complete plasma and breast milk methadone concentration data on the first 2 days of life, in addition to the onset of the true induction of lactation that generally occurs after day 2.[43]

Only 1 infant in this study had NAS symptomatology severe enough to require pharmacologic therapy, which is lower than published reports[44] and program norms.[30] The mother of this infant was on a moderate dose of methadone (60 mg), did not take psychotropic medications, and did not smoke. This finding is not readily explainable. The pathophysiology of NAS is not well understood, and the numbers of participants in this study small. Methadone concentrations in breast milk are small and normally insufficient to prevent NAS.[20] A hypothesis for the finding of a lower rate of treatable NAS in this sample may be that the physiological requirements of breastfeeding, such as skin-to-skin contact, small frequent feedings, and the mother's constant presence, may be beneficial enough for the infant who has mild NAS symptomatology to avoid pharmacologic therapy for NAS.

Limitations of this study include the small numbers of participants and inconsistent sampling in the first day of life due to the difficult nature of expressing and collecting colostrum. Only breast milk in the immediate neonatal period was studied, which may not be generalizable to older breastfeeding infants of methadone-maintained mothers. A further limitation of this study is the designations of days of life after birth, due to varying birth times and constrictions on prescribing methadone in this period.

This research demonstrated that concentrations of methadone in breast milk, even at peak maternal plasma methadone levels, are low in the perinatal period. These data support the recommendation of breastfeeding for methadone-maintained women. Furthermore, the findings that maternal methadone dose was unrelated to plasma and breast milk methadone concentrations support the recommendation that methadone-maintained women should not be denied breastfeeding their infants based on their required dose of methadone. The finding that methadone concentration increased over the first 4 days of life for the peak postfeed specimens warrants consideration. More research is needed to determine if methadone concentration increases over longer periods of time for infants of methadone-maintained, lactating mothers and to evaluate the effects of small amounts of methadone on the developing infant.

Acknowledgments

The authors thank the participants, Vickie Walters, LGSW-C, Tammy Roberts, Erik Fitzgerald, Andrea Elko, PA-C, and Susan Doyle, RN, for their contributions to this work. This project was funded by NIH/NIDA grant K08 DA00495 awarded to the first author, and supported by the NIH/NIDA Intramural Research Program.

References

1. Finnegan, L.; Kandall, S. Maternal and neonatal effects of alcohol and drugs. In: Lowinson, JH.; Ruiz, P.; Millman, RB.; Langrad, JG., editors. Substance Abuse: A Comprehensive Textbook. Williams & Wilkins; Baltimore, MD: 1992. p. 628-656.
2. Gottheil E, Sterling R, Weinstein S. Diminished illicit drug use as a consequence of long-term methadone maintenance. J Addict Dis 1993;12:45–57. [PubMed: 8292639]
3. Newman R. Methadone treatment: defining and evaluating success. N Engl J Med 1987;317:447–450. [PubMed: 3614287]
4. Lowinson, J.; Marion, IJ.; Joseph, H.; Dole, VP. Methadone maintenance. In: Lowinson, J.; Ruiz, P., editors. Substance Abuse: Clinical Problems and Perspectives. Williams & Wilkins; Baltimore, MD: 1981. p. 550-561.
5. Mackie-Ramos R, Rice J. Group psychotherapy with methadone maintained pregnant women. J Subst Abuse Treat 1988;5:151–161. [PubMed: 3236389]
6. Kreek M. Medical complications in methadone patients. Ann N Y Acad Sci 1978;311:110–134. [PubMed: 369431]
7. Swan, N. NIDA Notes. National Institute on Drug Abuse, National Institutes of Health, U.S. Dept. of Health and Human Services; Bethesda, MD: 1994. Research demonstrates long-term benefits of methadone treatment; p. 3-5.
8. Catalano R, Gainey RR, Fleming CB, Haggerty KP, Johnson NO. An experimental intervention with families of substance abusers: one year follow-up of the focus on families project. Addiction 1999;94:241–254. [PubMed: 10396792]
9. Velez M, Jansson LM, Montoya I, Schweitzer W, Golden AS, Svikis D. Parenting knowledge among substance abusing women in treatment. J Subst Abuse Treat 2004;27:215–222. [PubMed: 15501374]
10. Finnegan L. Treatment issues for opioid-dependent women during the perinatal period. J Psychoactive Drugs 1991;23:191–201. [PubMed: 1765892]
11. Kandall S, Albin RS, Gartner LM, Lee KS, Eidelman A, Lowinson J. The narcotic dependent mother: fetal and neonatal consequences. Early Hum Dev 1977;1:159–169. [PubMed: 617308]
12. Dinges D, Davis M, Glass P. Fetal exposure to narcotics: neonatal sleep as a measure of nervous system disturbance. Science 1980;209:619–621. [PubMed: 7190326]
13. Mikhail M, Youchah J, DeVore N, Ho GY, Anyaegbunam A. Decreased maternal-fetal attachment in methadone-maintained pregnant women: a preliminary study. J Obstet Gynecol Neonatal Nurs 1995;31:156–164.
14. The American Academy of Pediatrics. The promotion of breastfeeding. Pediatrics 1982;69:654. [PubMed: 7079026]
15. The American Academy of Physicians. 1994-1995 Compendium of AAFP Positions on Selected Health Issues. The American Academy of Family Physicians; Kansas City, MO: 1996. Breastfeeding and infant nutrition.
16. The American Academy of Pediatrics. The American College of Obstetricians and Gynecologists. Maternal and Newborn Nutrition, Guidelines for Perinatal Care. American Academy of Pediatrics; Elk Grove Village, IL: 1992. p. 181
17. World Health Organization. Twenty-seventh World Assembly of the World Health Organization. World Health Organization; Geneva, Switzerland: 1974. Infant nutrition and breastfeeding.
18. Lawrence, R. Breastfeeding: A Guide for the Medical Profession. Vol. 4th ed.. Mosby; St Louis, MO: 1994.
19. American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776–789. [PubMed: 11533352]
20. Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. J Hum Lact 2004;20:62–71. [PubMed: 14974702]
21. Wolman I, Niv D, Yovel I, Pausner D, Geller E, David MP. Opioid-addicted parturient, labor, and outcome: a reappraisal. Obstet Gynecol Surv 1989;44:592–597. [PubMed: 2668814]
22. Ballard J. Treatment of neonatal abstinence syndrome with breast milk containing methadone. J Perinat Neonatal Nurs March;2002 :76–85. [PubMed: 11911622]

23. Kreek M, Schecter A, Gutjahr C. Analysis of methadone and other drugs in maternal and neonatal body fluids: use in evaluation of symptoms in a neonate of mother maintained on methadone. Am J Drug Alcohol Abuse 1974;1:409–419. [PubMed: 4619541]
24. Blinick G, Inturrisi CE, Jerez E, Wallach RC. Methadone assays in pregnant women and progeny. Am J Obstet Gynecol 1975;121:617–621. [PubMed: 1115163]
25. Kreek M. Methadone disposition during the perinatal period in humans. Pharmacol Biochem Behav 1979;11:7–13. [PubMed: 550136]
26. Pond S, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exper Ther 1985;233:1–6. [PubMed: 3981450]
27. Geraghty B, Graham EA, Logan B, Weiss EL. Methadone levels in breast milk. J Hum Lact 1997;13:227–230. [PubMed: 9341416]
28. Wojnar-Horton R, Kristensen JH, Yapp P, Ilett KF, Dusci LJ, Hackett LP. Methadone distribution and excretion into breast milk of clients in a methadone maintenance program. Br J Clin Pharmacol 1997;44:543–547. [PubMed: 9431829]
29. McCarthy J, Posey B. Methadone levels in human milk. J Hum Lact 2000;16:115–120. [PubMed: 11153342]
30. Jansson LM, Svikis D, Lee J, Paluzzi P, Rutigliano P, Hackerman F. Pregnancy and addiction: a comprehensive care model. J Subst Abuse Treat 1996;13:321–329. [PubMed: 9076650]
31. Li R, Darling N, Maurice E, Barker L, Grummer-Strawn LM. Breastfeeding rates in the United States by characteristics of the child, mother or family, the 2002 National Immunization Survey. Pediatrics 2005;115:1450–1451. [PubMed: 15867081]
32. Rose V, Warrington VO, Linder R, Williams CS. Factors influencing infant feeding method in an urban community. J Natl Med Assoc 2004;96:325–331. [PubMed: 15040514]
33. Kreek M. Plasma and urine levels of methadone. N Y State J Med 1973;23:2773–2777. [PubMed: 4520357]
34. Handelsman L, Cochrane KJ, Aronson MJ, Ness RA, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987;13:293–308. [PubMed: 3687892]
35. Galloway FR, Bellet NF. Methadone conversion to EDDP during GC-MS analysis of urine samples. J Anal Toxicol 1999;23:615–619. [PubMed: 10595849]
36. Alburges ME, Huang W, Foltz RL, Moody DE. Determination of methadone and its N-demethylation metabolites in biological specimens by GC-PICI-MS. J Anal Toxicol 1996;20:362–368. [PubMed: 8889671]
37. Neville M, Keller R, Seacat J, et al. Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. Am J Clin Nutr 1988;48:1375–1386. [PubMed: 3202087]
38. Hartmann P, Prosser C. Physiological basis of longitudinal changes in human milk yield and composition. Federation Proc 1984;43:2448–2453. [PubMed: 6373380]
39. Hoekelman, R.; Adam, HM.; Nelson, NM.; Weitzmann, ML.; Wilson, MH. Primary Pediatric Care. Vol. 4th ed.. Mosby; St Louis, MO: 2001.
40. Lawrence, RA.; Lawrence, RM. Biochemistry of Human Milk in Breastfeeding: A Guide for the Medical Professional. Elsevier Mosby; Philadelphia, PA: 2005. p. 105-170.
41. Loimer N, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend 1992;30:241–246. [PubMed: 1396105]
42. Wolff K, Boys A, Rostami-Hodjegan A, Hay A, Raistrick D. Changes to methadone clearance during pregnancy. Eur J Clin Pharmacol 2005;61:763–768. [PubMed: 16261362]
43. Kulsky J, Hartmann P. Changes in human milk composition during the initiation of lactation. Aust J Exp Biol Med Sci 1981;59:101–114. [PubMed: 7236122]
44. McCarthy J, Leamon MH, Parr MS, Anania B. Hi-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. Am J Obstet Gynecol 2005;193:606–610. [PubMed: 16150249]

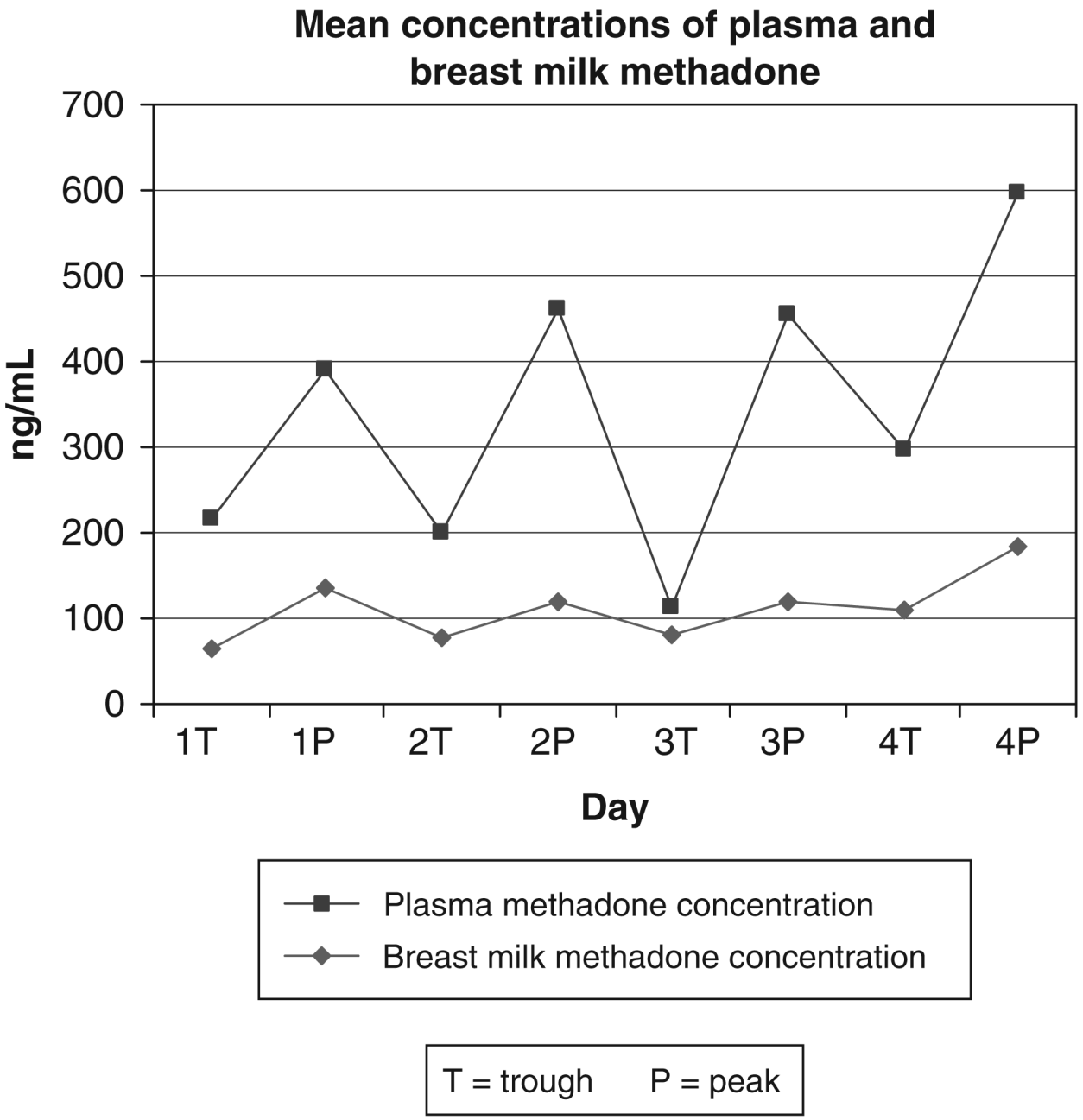

Figure 1.
Mean concentrations of plasma and breast milk methadone.

Table 1

Concentrations of Methadone in Breast Milk*

	N	*Range (ng/mL)*	*Mean (ng/mL) Concentration of Methadone ± SD*	*Mean Infant Dose Ingestible (mg/day ± SD)*
Day 1				0.006 ± 0.007
Trough				
Prefeed	7	27.1-179.0	82.3 ± 50.5	
Postfeed	4	31.5-130.5	64.8 ± 45.5	
Peak				
Prefeed	6	63.6-187.5	128.2 ± 51.1	
Postfeed	5	51.7-261.8	144.3 ± 79.6	
Day 2				0.018 ± 0.010
Trough				
Prefeed	10	21.0-217.9	76.1 ± 66.0	
Postfeed	8	20.6-225.1	80.2 ± 76.9	
Peak				
Prefeed	9	27.4-274.6	110.3 ± 80.3	
Postfeed	8	31.6-274.0	125.2 ± 86.6	
Day 3				0.039 ± 0.016
Trough				
Prefeed	12	38.1-241.5	79.5 ± 57.8	
Postfeed	12	42.1-169.5	80.1 ± 40.1	
Peak				
Prefeed	12	45.1-193.3	113.5 ± 46.8	
Postfeed	10	52.3-182.8	123.4 ± 35.0	
Day 4				0.084 ± 0.036
Trough				
Prefeed	12	42.6-229.7	101.8 ± 55.9	
Postfeed	12	49.4-314.2	114.7 ± 84.2	
Peak				
Prefeed	12	79.9-281.4	166.0 ± 67.8	
Postfeed	12	101.5-301.6	199.5 ± 66.7	

*Concentration of methadone in breast milk increased over time for the peak postfeed sampling time ($t(22) = 2.40$, $P = .0255$).

Table 2

Concentrations of Methadone in Maternal Plasma

	N	*Range (ng/mL)*	*Mean (ng/mL) Concentration of Methadone ± SD*
Day 1			
Trough	12	47.0-409.0	149.4 ± 105.1
Peak	12	117.0-441.0	253.2 ± 101.0
Day 2			
Trough	12	45.0-247.0	120.4 ± 70.7
Peak	10	80.0-592.0	343.7 ± 162.6
Day 3			
Trough	12	71.0-352.0	140.9 ± 78.16
Peak	12	178.0-707.0	337.3 ± 146.6
Day 4			
Trough	12	111.0-384.0	188.2 ± 73.5
Peak	11	176.0-694.0	414.2 ± 163.3

Table 3

Mean Breast Milk to Plasma Methadone Concentration Ratios

	N	*Range*	*Mean Ratio ± SD*
Day 1			
Trough	7	0.2-1.5	0.8 ± 0.5
Peak	6	0.3-1.2	0.6 ± 0.3
Day 2			
Trough	10	0.1-2.7	0.9 ± 0.8
Peak	8	0.1-0.7	0.4 ± 0.2
Day 3			
Trough	12	0.2-2.1	0.7 ± 0.5
Peak	12	0.2-0.8	0.4 ± 0.2
Day 4			
Trough	12	0.2-1.7	0.6 ± 0.4
Peak	11	0.2-0.9	0.4 ± 0.2